Association of low serum total cholesterol with major depression and suicide

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Background It has been suggested that low serum total cholesterol is associated with an increased risk of suicide.

Aims To study the association between serum total cholesterol, depression and suicide using versatile, prospective data.

Method A total of 29 133 men aged 50–69 years were followed up for 5–8 years. Baseline blood samples were analysed for serum total and high-density lipoprotein cholesterol concentrations. Self-reported depression was recorded, data on hospital treatments due to depressive disorders were derived from the National Hospital Discharge Register and deaths from suicide were identified from death certificates.

Results Low serum total cholesterol was associated with low mood and subsequently a heightened risk of hospital treatment due to major depressive disorder and of death from suicide.

Conclusions Our results suggest that low serum total cholesterol appears to be associated with low mood and thus to predict its serious consequences.

Declaration of interest A trial contract (N01-CN-45165) with the National Cancer Institute.

There has been some debate as to whether lowering serum total cholesterol is associated with an increased risk of suicide. Randomised controlled trials using cholesterol-reducing treatments have found no evidence of excessive risk (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd *et al*, 1995). In contrast, the relationship between serum cholesterol and mortality from either accidents or suicide has been discovered in community cohorts (Law *et al*, 1994; Zureik *et al*, 1996). Thus, the association between low cholesterol and death from suicide remains obscure.

METHOD

This study was based on the trial cohort of a randomised double-blind placebo-controlled primary prevention trial to test the hypothesis that α-tocopherol and β-carotene supplements reduce the incidence of lung and other cancers (ATBC Cancer Prevention Study Group, 1994). The study participants were recruited from the total male population of 50–69 years of age residing in south-western Finland (n=290 406) in 1985–1988. These men were sent a questionnaire on current smoking and willingness to participate in the trial. Smokers of at least five cigarettes per day and who were willing to enrol were then sent an invitation to visit their local study centre for further evaluation of their eligibility. A previous diagnosis of cancer, current severe angina with exertion, chronic renal insufficiency, cirrhosis of the liver, alcohol dependence or a disorder limiting participation in the long-term trial were grounds for exclusion. A total of 29 133 men were randomly assigned to receive supplements of α-tocopherol, or β-carotene, or both, or placebo, in a 2×2 factorial design. The review boards of the participating institutions approved the study. All subjects gave written informed consent prior to randomisation.

At baseline, subjects completed a questionnaire about their general background and medical and smoking histories, including two items on anxiety and depression experienced in the past four months. Diet and alcohol consumption were assessed in a detailed diet-history questionnaire (Pietinen *et al*, 1988), and height and weight were measured. Blood samples were taken at baseline and after three years of follow-up. Concentrations of serum total and high-density lipoprotein (HDL) cholesterol were assessed using an enzymatic method (CHOD/PAP, Boehringer Mannheim, Mannheim, Germany). The participants made three follow-up visits to their local study centres annually for 5–8 years. They reported on a questionnaire whether they had felt anxiety or depression since the preceding visit.

End-point assessment

The study end-points were self-reported depression, hospital treatment due to major depressive disorder, and death from suicide. Feelings of depression were enquired about at baseline and at each follow-up visit until drop-out or trial closure in 1993. When analysing the association between baseline cholesterol concentrations and subsequent self-reports of depression, the first follow-up report was considered.

Data on hospital treatment due to depressive disorders were derived from the National Hospital Discharge Register, which covers in-patient admissions to all medical and psychiatric hospital beds in Finland. The accuracy of the Register compared with medical records is excellent, with the data being identical in about 95% of the primary diagnoses (Keskimäki & Aro, 1991). The diagnoses were coded according to the International Classification of Diseases (ICD–8; World Health Organization, 1968) up to the end of 1986 and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM–III–R; American Psychiatric Association, 1987) thereafter. When analysing the association between baseline cholesterol concentrations and subsequent hospital treatments due to major depressive disorder, the first treatment period by the end of 1994 was considered. Information on hospital treatment for depressive disorders was also available for the drop-outs.

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The follow-up of survival extended to the end of 1994. Data on deaths were derived from the Central Population Register, and the cause of death was reviewed from death certificates. Suicide assigned as the cause of death was considered as the end-point.

Statistics

Cox's proportional hazards regression model was used to estimate the relationships between baseline cholesterol concentrations and the first occurrence of self-reported depression, the first hospital treatment period due to major depressive disorder and death from suicide. Significance of variables was tested using likelihood ratio statistics. Known important risk factors for major depression and suicide were entered into the models as covariates, with continuous variables divided into tertiles. A Kaplan–Meier cumulative-mortality plot was computed for suicide among the subjects according to the three categories of baseline serum total cholesterol. In addition, models were formulated to estimate the relationships between baseline cholesterol concentrations and all violent deaths, or violent deaths exclusive of suicide.

The concentration of serum total cholesterol was modelled as three categories (<5, 5–7 and >7 mmol/l), according to the Finnish National Consensus Guidelines: values in the high category indicate the need for treatment and those in the low category are considered the goal of cholesterol-lowering treatment. The estimated relative risk and the 95% confidence interval (95% CI) were calculated, with <5 mmol/l as the reference value. Dietary factors were adjusted for energy intake in the models. The interactions between baseline values and time of follow-up were tested using the Poisson regression model.

RESULTS

The mean (s.d.) age of the 29 133 participants was 57.7 (5.1) years and the concentrations of serum total and HDL cholesterol were 6.23 (1.17) and 1.17 (0.31) mmol/l, respectively, at baseline. There were 3924 men with a baseline serum total cholesterol level of <5 mmol/l, 18 356 men with a level of 5–7 mmol/l and 6818 men with a level of >7 mmol/l.

At study entry, 4314 (15%) men reported feeling depressed during the preceding four months and 6498 (22%) complained of anxiety. The age-adjusted risk of reporting depression at baseline was significantly associated with the level of baseline serum total cholesterol ($P<0.0001$), the relative risks (95% CI) being 1.00 (reference), 0.92 (0.87–0.98) and 0.88 (0.82–0.94) in categories of <5, 5–7 and >7 mmol/l, respectively. Although the men reporting depression had lower mean serum total cholesterol than the others, they reported similar dietary intakes of energy, fat and carbohydrates than the remaining men (Table 1). There was no significant association between serum total cholesterol and self-reports of anxiety at baseline. The trial

Table 1 Serum total and high-density lipoprotein (HDL) cholesterol, body mass index and dietary intake by self-reported depression at baseline

Baseline variable	Depressed (n=4314)		Not depressed (n=24 790)		F-test P value
	Mean	s.d.	Mean	s.d.	
Total cholesterol (mmol/l)	6.17	1.19	6.25	1.16	<0.0001
HDL cholesterol (mmol/l)	1.18	0.33	1.17	0.31	0.03
Body mass index (kg/m^2)	26.3	3.9	26.3	3.8	0.6
Carbohydrates (g/day)	308	98	303	95	0.007
Fat (g/day)	125	42	123	41	0.006
Energy (kcal/day)	2877	813	2804	782	<0.0001

Table 2 Incidence per 1000 person-years and relative risk (RR) of subsequent self-reported depression, hospital treatment due to major depression and death from suicide by baseline serum total and high-density lipoprotein (HDL) cholesterol

End-point		Baseline total cholesterol (mmol/l)			Baseline HDL cholesterol (mmol/l)		
		<5	5–7	>7	<1.01	1.01–1.25	>1.25
Self-report	No. of cases	1288	5869	2128	3079	3085	3121
	Incidence	98.8	88.7	83.6	87.7	86.3	92.3
	RR[1]	1.00	0.90	0.85	1.00	0.98	1.05
	95% CI		0.85–0.95	0.79–0.91		0.94–1.03	1.00–1.11
	RR[2]	1.00	0.95	0.94	1.00	1.01	0.99
	95% CI		0.90–1.02	0.88–1.01		0.96–1.06	0.93–1.05
Hospital	No. of cases	49	178	53	97	91	92
	Incidence	1.78	1.34	1.06	1.39	1.28	1.31
	RR[1]	1.00	0.75	0.59	1.00	0.92	0.94
	95% CI		0.55–1.03	0.40–0.87		0.69–1.23	0.71–1.25
	RR[2]	1.00	0.77	0.64	1.00	1.06	1.00
	95% CI		0.55–1.08	0.42–0.96		0.78–1.45	0.71–1.40
Suicide	No. of cases	25	67	19	29	35	47
	Incidence	0.91	0.50	0.38	0.42	0.49	0.67
	RR[1]	1.00	0.55	0.42	1.00	1.18	1.61
	95% CI		0.35–0.88	0.23–0.76		0.72–1.94	1.01–2.56
	RR[2]	1.00	0.55	0.42	1.00	1.30	1.51
	95% CI		0.34–0.88	0.22–0.78		0.77–2.18	0.89–2.56

1. The non-adjusted relative risks using the univariate Poisson regression model.
2. The relative risks were adjusted for age, body mass index, carbohydrate intake, consumption of alcohol, education, marriage, self-reported anxiety, self-reported depression and smoking using the multivariate Cox's proportional hazards regression model. Significance of baseline serum total cholesterol levels using the likelihood ratio test was P=0.3 for self-reported depression, P=0.1 for hospital treatment due to major depression and P=0.02 for death from suicide.

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supplementation had no influence on the main outcome measures.

A total of 9285 men reported feeling depressed at least once during the follow-up (Table 2). The relative risks of subsequent self-reported depression in men with baseline serum total cholesterol levels of <5, 5–7 and >7 mmol/l were 1.00, 0.90 and 0.85, respectively (P=0.0005). This association lost its significance after adjustment for other risk factors (P=0.1).

A total of 280 men were hospitalised due to major depressive disorder during the follow-up (Table 2). The relative risks of hospital treatment due to major depressive disorder according to baseline serum total cholesterol levels of <5, 5–7 and >7 mmol/l were 1.00, 0.75 and 0.59, respectively (P=0.01). After adjustment for other risk factors, the association between serum total cholesterol and the risk of hospital treatment due to major depressive disorder was attenuated but remained significant (P=0.04).

A total of 111 men committed suicide during the follow-up of 211 010 person-years. The relative risks of death from suicide in men with baseline serum total cholesterol levels of <5, 5–7 and >7 mmol/l were 1.00, 0.55 and 0.42, respectively (P=0.006), and after adjustment for other risk factors a significant association persisted between baseline serum total cholesterol and the suicide risk (P=0.007; see Table 2 and Fig. 1). This association was slightly attenuated among suicides committed more than four years after the baseline compared to earlier suicides. There was no significant association between the change in serum total cholesterol from baseline to three years of follow-up and the subsequent risk of death from suicide. The relative risks of death from suicide in men with baseline serum HDL cholesterol levels of <1.01, 1.01–1.25 and >1.25 mmol/l were 1.00, 1.18 and 1.61, respectively (P=0.03).

Because death from suicide is included in violent deaths, we also examined the association between violent deaths and baseline cholesterol level. There were 89, 260 and 88 violent deaths in men with baseline serum total cholesterol levels of <5, 5–7 and >7 mmol/l, respectively. The adjusted relative risks (95% CI) of violent deaths were 1.00 (reference), 0.62 (0.48–0.80) and 0.57 (0.42–0.79), respectively (P=0.0008). The adjusted relative risks (95% CI) of violent deaths exclusive of suicide were 1.00 (reference), 0.65 (0.48–0.89) and 0.64 (0.44–0.92), respectively (P=0.02).

DISCUSSION

Our results support previous data relating low cholesterol to low mood. We found that men reporting depression at baseline had lower mean serum total cholesterol compared to those with no self-reported depression, but that low baseline serum total cholesterol was not associated with subsequent self-reported depression. This suggests that the primary event is the occurrence of depression. Depression then tends to result in a declining serum total cholesterol level, and the lower serum total cholesterol was related to the subsequent risk of hospitalisation due to major depression and to death from suicide.

As a new finding, higher baseline serum HDL cholesterol was also associated with the risk of death from suicide.

Validity of self-report of depression

We were able to show that low serum total cholesterol was associated with suicide risk even after controlling for self-reported depression at baseline. It is likely that the gain in sensitivity achieved by using a self-report questionnaire to measure depression resulted in loss of specificity. However, asking only two questions may be as effective as using many more for detecting depression, because a two-item case-finding instrument displayed test results similar to those using validated multi-item instruments (Whooley *et al*, 1997). Hence, to some extent, our results can be considered to uphold the validity of self-reported data for identifying depression.

Control of confounding factors

We adjusted our models of the suicide risk for consumption of alcohol, which is suggested to lower total cholesterol levels. We found the correlation between serum total cholesterol and alcohol intake to be low. There was a trend for higher HDL cholesterol levels to be associated with increased risk of suicide. Because no plausible explanation is available to link HDL cholesterol level to death from suicide, it is likely that high HDL cholesterol reflects higher alcohol intake, which is known to be a true risk factor for suicide (Harris & Barraclough, 1997). It is possible that subjects denying their alcohol intake were at the greatest risk of suicide. This assumption is supported by the apparent suicide risk among subjects reporting complete abstinence.

Another factor that lowers serum total cholesterol and might lead to suicide is cancer. However, we found that the relationship between low baseline serum total

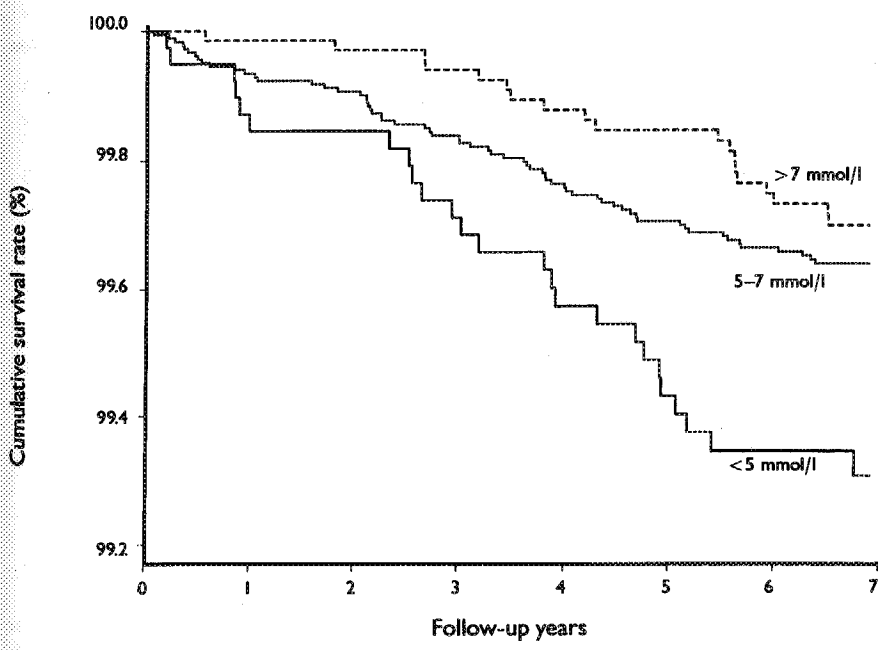

Fig. 1 Cumulative survival rate by baseline serum total cholesterol (the Kaplan–Meier curve). Log-rank test P=0.0091.

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cholesterol and death from suicide remained similar after excluding subjects with cancer diagnosed within five years from serum sampling. Misclassification of death from suicide is an unlikely explanation, because non-suicidal violent deaths showed a similar association with low cholesterol level.

Research findings

There is speculation about how a low cholesterol level could be related directly to suicide (Boston *et al*, 1996). A low content of cholesterol within cell membranes has been shown experimentally to decrease the number of serotonin receptors (Engelberg, 1992). It has been hypothesised that lowered levels of serum total cholesterol may lead to a decrease in brain serotonin and, as a consequence, to poor control of aggressive impulses (Steegmans *et al*, 1996). This idea has been supported by the finding that serum total cholesterol is abnormally low after attempted suicide (Gallerani *et al*, 1995). Dietary factors, such as intake of carbohydrates, in addition to defects in metabolism of glucose and lipids may be involved.

Clinical view

We conclude that low serum total cholesterol appears to be associated with low mood. We also suggest that low serum total cholesterol predicts the occurrence of more severe conditions indicative of poor outcome, such as hospitalisation due to major depressive disorder and death from suicide. Both low and declining levels of serum total cholesterol deserve attention in primary care and in psychiatry, regardless of whether they serve only as a marker of excess mortality. Measurement of serum total cholesterol might be helpful for the clinician in the search for and recognition of depression.

CLINICAL IMPLICATIONS

- Low serum total cholesterol at baseline is associated with a heightened risk of major depressive disorder.
- Low serum total cholesterol at baseline is associated with a heightened risk of death from suicide, even after adjusting for risk factors.
- Measurement of serum cholesterol might aid in the recognition of depressed mood and result in preventing its serious consequences.

LIMITATIONS

- Concentrations of serum cholesterol were not repeatedly assessed in parallel to depression experienced at follow-up visits.
- The gain in sensitivity achieved by using a self-report questionnaire to measure depression may have resulted in loss of specificity.
- Although the estimated risk of suicide was controlled for consumption of alcohol, some residual confounding was still suggested to exist.

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